Diagnosis and treatment of endometriosis. A review

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Diagnosis and treatment of endometriosis

A review

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The correct approach for endometriosis management is still unclear. This review explores recent data concerning diagnosis and treatment of endometriosis, trying to define guidelines for the most appropriate diagnostic approach and therapeutic regimen. At present, laparoscopy is still considered the gold standard in endometriosis diagnosis. The risks and the diagnostic limitations of laparoscopy and the inaccuracy of clinical examination justify the considerable efforts made to improve the diagnosis with imaging techniques. The therapeutic approach is still far from being defined as causal and focuses on management of clinical symptoms of the disease rather than on the disease itself. A first-line medical therapy should be tried in patients with pelvic pain not asking for a pregnancy. Surgical treatment is considered the best treatment for women with pain and or pelvic mass who wish to become pregnant in a short time. For infertile patients, medical therapy has a limited role. The 2 treatment options include surgery or *in vitro* fertilization (IVF). According to our results, it seems that correct management of infertile women with endometriosis is a combination of surgery and IVF in women who did not obtain post-surgery pregnancy spontaneously.

Key words: **In vitro fertilization - Endometriosis, diagnosis - Endometriosis, therapy.**

Endometriosis is a common, benign, oestrogen-dependent, disorder associated with pelvic pain and infertility. It is characterized by the presence of uterine endometrial tissue outside the normal location, mainly on the pelvic peritoneum, but also on the ovaries in the rectovaginal septum, and, more rarely, on extra-pelvic organs.

The increasing clinical and experimental research interest in endometriosis is based on several factors a still controversial: pathogenesis; different macro and microscopical appearances; an often modified and limiting staging system; a wide range of available diagnostic approaches; a not yet universally therapeutic approach.

The comparison of an often invalidating symptomatology and the likely interference on integrity of the reproductive system, in the patients affected by endometriosis, make European Parliament consider endometriosis as a social disease.

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Epidemiology

Despite all surveys carried out on the endometriosis, we still do not have a clear epidemiologic picture of such pathology. In fact, most of the studies focus on groups of pa-

tients in hospitals and do not take into account the prevalence of the pathology in the general population. It is believed that the endometriosis is a clinical status which affects 1 out of 10 women in the European Union.

According to Schifrin *et al.*, the prevalence of endometriosis in infertile women undergoing laparoscopy is between 20% and 40%, while it is 2% to 10% for a general female population in reproductive age.[1]

Actual incidence rates are poorly defined, but the study of Houston *et al.* in Rochester, Minnesota from 1970 to 1979 suggests a figure of 1.6/1 000 woman/years.[2]

In Italy an epidemiologic study has been performed by the Gruppo Italiano per lo Studio dell'Endometriosi (GISE) showing a clear picture of endometriosis spreading. The percentages of disease have turned out to be of 30%, 45%, 35% and 12% in sterile patients, patients with pelvic pain, patients with benign ovarian pathology and in patients with myoma respectively.[3]

It seems that the frequency of endometriosis is increasing, but it is still unclear whether this is due to a real increase of incidence that could be partially explained by changed reproductive habits, pollution, or improved diagnostic possibilities including the growing use of laparoscopy and the acknowledgment of atypical lesions.[4]

Diagnosis

Endometriosis was first noted by von Rokitansky in 1860 and termed "adenomyoma".[5] It was Sampson's classic publication in 1920 [6] that described the variable appearance of endometriotic implants discovered at the time of exploratory laparotomy.[7] Thereafter, histological confirmation of endometrial glands and stroma in extrauterine sites was considered the gold standard for the diagnosis of endometriosis.

An accurate clinical examination can indicate endometriosis. The improvement of the various image and endoscopic techniques, as well as sierologic ones, allows correct diagnosis of the desease.

Histology

Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. Whether histology should be obtained, if peritoneal disease alone is present is controversial: visual inspection is usually adequate but histological confirmation of at least one lesion is ideal. In cases of ovarian endometrioma > 3 cm in diameter, and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy.[8]

Laparoscopy

At present laparoscopy is still considered as the gold standard diagnostic test looking for evidence of all types and stages of endometriosis.[8, 9] The advent of laparoscopic techniques has allowed diagnosing endometriosis by visualization of typical and atypical lesions. Frequency of diagnosis of endometriosis at laparoscopy has increased dramatically.[10] The terminology used to describe peritoneal lesions varies:[11]

Pink or red lesions:

— papular or vesicular with serous or haemorrhagic content;
— flame-like lesion;
— neoangiogenesis.

Black lesions:

— classic puckered, blue/blue—black powder-burn (gun shot) lesions;
— variable amount of vascularization and fibrosis.

White lesions:

— white scarring.

Free-floating, microvascularized or haemorrhagic adhesions.

Peritoneal defects (with implants on border or in the defect):

— circular or oval;
— cribriform.

However, reliance on laparoscopic visualization of lesions in order to make a diagnosis may lead to inaccurate conclusions. The positive predictive value of visual findings consistent with endometriosis *versus* histological confirmation of endometriosis ranges

from 14% to 65% depending on the anatomic site and from 0% to 76% depending on lesion type.[12] For sites such as the posterior cul-de-sac, the positive predictive value is relatively high, whereas for unusual sites such as the psoas muscle, the positive predictive value is very low. The overall positive predictive value for laparoscopic visualization is 43–45%.[12, 13] With a low positive predictive value for visualization, the accuracy of American Fertility Society staging at the time of laparoscopic evaluation must be questioned.[12]

Laparoscopy also has major limitations, particularly for the diagnosis of posterior pelvis, bowel, and bladder endometriosis.[11] Moreover non-pigmented [14] and subperitoneal [15] lesions can't be detected by laparoscopy.

A variety of pathologic lesions are confused visually with endometriosis implants. Endosalpingiosis, mesothelial hyperplasia, hemosiderin deposition, hemangiomas, residual carbon from previous ablation procedures, reactions to oil-based radiographic dyes, inflammatory changes, and splenosis all may be mistaken for endometriosis.[10]

Although laparoscopy is regarded as the gold-standard diagnostic test for endometriosis, diagnostic laparoscopy is associated with 0.06% risk of major complications and this risk is increased to 1.3% in operative laparoscopy.[16]

Clinical examination

Due to the fact that laparoscopy is an invasive approach, clinical examination is still crucial in endometriosis diagnosis.

Anamnesis

Typically endometriosis causes pain and infertility, although the 20-25% of the patients is asymptomatic.[17] Other symptoms can indicate endometriosis:

— dysmenorrhea (60%);[18]
— deep dyspareunia (40-50%);[18]
— chronic pelvic pain (40-50%);[18]
— infertility;
— severe menstrual and irregular flow and/or premenstrual spotting;
— dysfunctional uterine bleeding;
— tenesmus, dyschezia, hematochezia, costiveness or diarrhea;
— dysuria, pollakiuria, micro- or macroscopic hematuria;
— pain and feeling of heavy lumbo-sacral column and/or legs;
— nausea, lethargy, chronic fatigue;
— premenstrual tension;
— any cyclical pain affecting other organs;
— hemoptysis, scapular and thoracic pain;
— possible acute abdomen.

Studies have reported that a wide range (14–67%) of infertile women who undergo laparoscopy have endometriosis.[19-21]

Although women with and without endometriosis have a similar prevalence of dysmenorrhea, patients may be more likely to have more severe symptoms.[18, 22, 23] Severe dysmenorrhea is better than dyspareunia and pelvic pain in predicting endometriosis, with 63% PPV and 95% NPV.[18, 19-24]

Consequently pain, and mainly severe dysmenorrhea, represents so an important symptom of endometriosis that leads to the diagnostic suspicion of disease or recurrence.

Calhaz-Jorge *et al.* have recently published a cohort study indicating that the presence of endometriosis can be predicted from the medical history. The prevalence of endometriosis in subfertile women is related to race, body mass index, irregular menstrual cycles, intensity of menstrual flow, dysmenorrhoea, chronic pelvic pain, obstetric history, oral contraceptive (OC) use and smoking habits. These data should be used in the decision to perform laparoscopy at an early stage or a later stage in the work-up for subfertility.[25]

Physical examination

Most women with endometriosis have completely normal pelvic examinations.[26] In a study of women presenting for laparoscopy because of infertility or pelvic pain, the sensitivity, specificity, and PPV of focal pelvic tenderness to predict endometriosis was 79%, 32%, and 64%, respectively. Focal tenderness was most highly specific at the uterosacral ligaments and cul-de-sac pelvic zones, with

TABLE I.—*Ultrasound accuracy studies.*

Authors	Number	Size (mm)		Sensitivity	Specificity
		Mean	Range		
Kurjak *et al.*[28]	103	55	18-160	84	97
Guerriero *et al.*[29]	29	40	SD=10	84	95
Alcazar *et al.*[30]	27	Unknown		89	91
Guerriero *et al.*[31]	58	40	SD=16	81	96

83% PPV when these locations were considered.[27] Koninckx *et al.* reported that painful nodularities found at pelvic examination during menstruation were highly predictive of deep endometriosis, ovarian endometriosis, or severe cul de sac disease with 79% sensitivity and 92% specificity.[28]

Nevertheless, no single constellation of symptoms and findings is pathognomonic of endometriosis. Presentation of pathology is so variable and there is considerable overlap with other conditions such as irritable bowel syndrome and pelvic inflammatory disease. As a result there is often delay between symptoms onset and surgical diagnosis.[8, 9]

Imaging techniques

The risks and the diagnostic limitations of laparoscopy and the inaccuracy of clinical examination justify the considerable efforts made to improve the diagnosis with imaging techniques.

Imaging studies, such as ultrasonography, magnetic resonance (MR) imaging, and computed tomography, are useful only in the presence of a pelvic or an adnexal mass. All imaging techniques have a low sensitivity for the diagnosis of peritoneal and ovarian implants and adhesions. In these cases laparoscopy remains the only diagnostic tool, despite the above-mentioned limits.[11]

TRANSVAGINAL SONOGRAPHY

Since the end of the 80s transvaginal sonography has spread and has been proven to be highly sensitive during the analysis of pelvic masses and especially endometriosis. In a recent review on the accuracy of ultrasound in the diagnosis of endometriosis, Moore *et al.* identified 38 papers related to the diagnosis of endometriosis by ultrasound scan, but considered only 7 studies sufficiently well done for further analysis. The authors concluded that transvaginal ultrasound is a useful test to make and to exclude the diagnosis of an ovarian endometrioma.[29] However, the size of the endometrioma in these studies was either not stated or ranged from 18 to 160 mm (Table I).[30-33]

Therefore, transvaginal ultrasound might be accurate only for identifying endometriomata of 2 cm or more. In addition, the specificity is likely to be reduced in patients with a high risk of lutein cysts, such as patients with postoperative recurrent hemorrhagic cysts. Up to 73% of the recurrent hemorrhagic cysts after surgery for endometrioma prove to be dysfunctional cysts.[11]

Ovarian endometriomas are typically cystic structures that contain low-level, homogeneous internal echoes consistent with old blood.[34] Whether Doppler ultrasound adds to the diagnostic efficiency of transvaginal ultrasound remains uncertain. Guerriero *et al.* reported that endometriomata are associated with poor blood supply, whereas non-endometriomata, and particularly malignant tumors are characterized by a rich vascularization.[35] A typical vascular pattern for the endometrioma was described as pericystic flow at the level of the ovarian hylus.[32]

The low invasivity, the reduced cost, and the high specificity and sensitivity make transvaginal sonography a first-level test in the study of endometriomas.[9] Moreover, transvaginal sonography is very important in the diagnosis of endometriosis involving the bladder or rectum.[8] Such a method requires a high accuracy in execution and qualified physicians

Magnetic Resonance imaging

— *I-II stages*

Superficial peritoneal and ovarian endometriosis is not detectable by transvaginal sonography. MR imaging using fat saturation can detect up to 50% of small, hemorrhagic lesions measuring not more than 5 mm [35] and allows then diagnose of mild disease in 75% of cases.[36] The poor diagnostic accuracy of MR imaging for superficial endometriosis can be accounted for by:

— the small size of the implants;
— the cross-sectional images taken at 5 mm intervals;
— the different types of lesion (red, black and white) containing different amounts of endometriotic components, blood and fibrosis;
— the possible confusion with structures such as blood vessels, iso intense pelvic organs (such as the small bowel or rectum), adhesions and the sequel of previous surgery.

Thus MR is, in our opinion, an excessively fallible technique in diagnosing adhesions and superficial peritoneal lesions, compared with laparoscopy.

— *III-IV stages*

In endometriomas diagnosis, MR reached a sensitivity of 90% and a specificity of 98%.[37] Moreover it allows a detailed description of endometriomas, with exact measures by multidirectional cross-sectional images. Despite this, MR is seldom used in diagnosing endometriomas since nowadays transvaginal ultrasound is useful in studying all details, including vascularization.

Infiltrating deep endometriosis implants of posterior cul-de-sac and of the utero-sacral ligaments is a field of interest for MR, since it permits identifying deep endometriosis that cannot be seen with laparoscopy.[38]

Another field of interest for MR is intestinal endometriosis. The gastrointestinal tract is the most common site of extrapelvic disease, involved in up to 37% of women with endometriosis.[22, 39, 40] Although intestinal endometriosis is usually asymptomatic and often clinically not important, serious complications can occur.[41]

Bowel radiographic evaluations (such as double-contrast barium enema) in association with colonoscopy show abnormalities of the bowel wall and a normal mucosal profile contrary to what happens in the carcinoma. Extrinsic compression, extra-mucosal masses, fixation, sub-mucosal nodularity can easily be seen, although these lack of specificity and accuracy.[42]

Endoscopic ultrasound (EUS), nowadays not yet a widespread technique, is an accurate and minimally invasive test to detect rectosigmoid involvement preoperatively.[43]

If there is clinical evidence of deeply infiltrating endometriosis, ureteral, bladder, and bowel involvement should be assessed. Consideration should be given to performing MR imaging or ultrasound (trans-rectal and/or trans-vaginal and/or renal), with or without IVP and barium enema studies depending upon the individual circumstances, to map the extent of disease present, which may be multi-focal.[8] MR is indicated to study extraperitoneal locations of endometriosis.[9]

Laboratory testing

No laboratory findings are particularly helpful in making or confirming a diagnosis of endometriosis. An association between endometriosis and elevated serum CA-125 levels has been reported, and the CA-125 level may be of value in the woman with severe endometriosis, but assessment of CA-125 is of limited value in detecting women with minimal or mild disease.[44] Among women with endometriosis, a normal CA-125 level neither confirms the absence of endometriosis nor predicts recurrence.[45]

The test's performance to diagnose all disease stages was limited: the estimated sensitivity was only 28% for a specificity of 90%. The test's performance for moderate-severe endometriosis was better: a specificity of 89%, the sensitivity 47%. The routine use of serum CA-125 testing, particularly in subfertile patients, may be justified to identify a sub-group of women who are likely to benefit from early laparoscopy. It may, however, serve as a

useful marker for monitoring the effect of treatment once the diagnosis of endometriosis has been established.[9]

Other markers have been proposed as possible tools in the diagnosis of minimal-mild endometriosis (Ca 19-9, SICAM-1, PP14, IL6, TNF, autoantibodies, EGR-1, P450 aromatase, PP14). Except for serum interleukin (IL)-6 and peritoneal fluid tumor necrosis factor (TNF)-alpha levels, the diagnostic accuracy of other markers of endometriosis was either similar or worse than that of CA-125.[46]

In a recent study Kafali *et al.* compared increasing serum Ca-125 levels in women affected by endometriosis with patients having normal laparoscopic findings, during menstruation. In both groups Ca-125 levels turned out to be significantly higher during menstruation than during the rest of the cycle, with a significant higher increase among patients affected by endometriosis. If we consider a cut-off value of 83% (percentage increment of Ca-125 level), endometriosis can be diagnosed with a sensitivity of 93% and specificity of 92%.[47]

Therapeutic approach

The therapeutic approach is still far from being defined as causal and focuses on management of clinical symptoms of the disease rather than on the disease itself. Endometriosis pathogenesis is a source of controversy. No treatment has been shown to prevent recurrence. Recurrence rates vary considerably following different treatment modalities. The fact that no definitive therapeutic approach has turned out to be the most effective among all, shows the limited knowledge of endometriosis.

Medical treatment options

Most medical treatments for women with endometriosis are based on the consensus that endometriosis is a hormonally responsive disease. Two physiologic conditions, pregnancy and menopause, are often associated with resolution of signs and symptoms of endometriosis. Pharmacological analogues of these conditions are pseudopregnancy, performed through administration of progestins or oral contraceptives (OCs), and pseudomenopause (suppression of endogenous oestrogen biosynthesis) produced by androgens and gonadotropin-releasing hormone (GnRH) analogues.

According to some opinions, a first-line medical treatment should be tried without a confirmatory laparoscopy in patients with pelvic pain who are not desirous of pregnancy, and do not have adnexal masses, on the condition that such a decision is supported by a physical examination, laboratory tests, and above all by the exclusion of other common causes of pelvic pain.[48]

Non-steroidal anti-inflammatory drugs

Although non-steroidal anti-inflammatory drugs (NSAIDs) do not directly treat endometriosis lesions, they long have been a role in the treatment of endometriosis-associated pain.[49-51] NSAIDs are particularly well suited for dysmenorrhea, because the symptom is mediated by prostaglandin synthesis.[52] By inhibiting cyclooxigenase, NSAIDs reduce prostaglandin production and alleviate pain.[53]

Nevertheless long-term NSAIDs use has significant side effects, including gastric ulceration, kidney damage and an anti-ovulatory effect when taken at mid-cycle.[8]

To avoid these serious side effects, a new generation of NSAIDs has been introduced that specifically inhibits cyclooxygenase-2 (COX-2). These medications (Celebrex, Vioxx) are no more effective at treating dysmenorrhea than naproxen or ibuprofen, but they have a much lower risk of gastric ulceration.[54-56] The main disadvantage of COX-2 inhibitors is high cost.[53]

Oral Contraceptives

There is a paucity of data relating to the use of OC preparations in the treatment of symptomatic endometriosis. Based on a favorable side-effect profile, as well as the high level of comfort expressed by most women and physicians, OCs should be the first-line of therapy for the medical treatment of women with endometriosis who do not wish to conceive at the time.[57]

PROGESTINS

The symptoms associated with endometriosis usually regress during pregnancy partly due of the action of progesterone. Long-term exposure of endometriotic lesions to progestins results in decidualization and atrophy. Progestins also downregulate the pituitary gland, leading to decreased ovarian biosynthesis and secretion of estrogen. The most common progestational agent used in the United States is medroxyprogesterone acetate. Twenty to 30 µg per day orally is the usual dosage, but investigators have reported use of doses as high as 50 mg per day.[58] A significant number of the women complaints of abnormal uterine bleeding, nausea, breast tenderness, fluid retention, and depression associated with the use of medroxyprogesterone acetate.[59] Depot medroxyprogesterone acetate is a contraceptive formulation that has been recommended for women with endometriosis and pain-related symptoms. When compared with treatment with danazol, depot medroxyprogesterone acetate was found to be equally effective.[60] A difficulty with depot medroxyprogesterone acetate is the high incidence of side effects such as bloating, weight gain, and depression that are experienced by 15–65% of treated patients.[58]

DANAZOL

Danazol, an impeded androgen derived from ethisterone, suppresses pituitary secretion of gonadotropins and inhibits ovulation. Danazol has been shown to relieve pain and result in clinical improvement in 55–93% of women treated for 6 months.[61] Weight gain, edema, decrease in breast size, acne, hirsutism, increased oiliness of the skin, and deepening of the voice, to name a few, are experienced in 85% of women. Danazol is effective in treating the symptoms and signs of endometriosis. However, its use is limited by the occurrence of androgenic side effects.[62]

For side effects experienced with both medroxyprogesterone acetate and danazol, discontinuation is most effective, even thought diuretics and antidepressants have been tried.

GNRH AGONISTS

GnRH agonists, administered in depot formulation, induce a hypo estrogenic state, and they have become a standard means of therapy for women with endometriosis. An 85-100% rate of improvement can be expected with GnRH analogue therapy.[58]

Comparative trials of various GnRH analogues and danazol have also been reported. In nearly all comparisons, danazol and GnRH analogues have similar effectiveness for improving pain during treatment and for maintenance of symptom relief (for at least 6–12 months) after the cessation of treatment.[58]

Side effects with GnRH analogues result from hypoestrogenism. Most patients (80-90%) experience hot-flashes and other common menopausal symptoms.[63, 64] GnRHa also have adverse effects on bone density and lipid profiles.[53] Treatment in association with combined oestrogen and progestagen add-back appears to be effective and safe in terms of pain relief and bone density protection.[65] However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.[8]

In conclusion, medical treatment, by inhibiting ovarian function, is effective in relieving endometriosis-associated pain. The choice between the various drugs (OC, progestogens, danazol, GnRHa) depends principally upon their side-effect profiles and costs because seems that relieve pain associated endometriosis equally well.[8, 9, 57, 62, 66, 67]

MEDICAL TREATMENT AND INFERTILITY

Medical therapy with either GnRH analogues or danazol does not improve fecundity.[68] Therapy with hormonal treatments decreases the chance of conception for the duration of therapy.

INTRA-UTERINE SYSTEM

The levonorgestrel intra-uterine system (LNG IUS) may be effective at reducing endometriosis associated pain,[69] but there is insufficient evidence to make recommendations.[8]

New therapeutic approaches

Important advances in pathogenesis of endometriosis have been made within the past few years that promise for the development of new therapeutic approaches to limit symptoms and to improve fertility.[70]

The immune system is believed to be involved in the pathogenesis of endometriosis, and a lack of adequate immune surveillance in the peritoneum is thought to be a cause of the disorder.[71] Sharpe-Timms *et al.* found a protein they called Endo I in endometriotic epithelial cells, which was not observed in eutopic endometrial epithelium.[72] This protein was structurally similar to haptoglobin. The protein bound to peritoneal macrophages, increased their production of interleukin 6, and reduced macrophage phagocytic capacity by blocking adherence. Moreover IL 6 upregulates endometriotic production of Endo I.[73] Taken together, these findings strongly support a role for haptoglobin in the pathogenesis of compromised immune surveillance in women with endometriosis, and they suggest potential targets for therapies for pain and infertility by inhibition of haptoglobin's actions.[70]

In women with endometriosis, the peritoneal fluid has high concentrations of cytokines, growth factors, and angiogenic factors, derived from the lesions themselves, secretory products of macrophages and other immune cells, and follicular fluid, after follicle rupture, in ovulating women.[74-77] Cytokines (IL1 and 8, TNFα, and IFNγ) act on chemotactic factors, which in turn recruit macrophages and T lymphocytes to the peritoneum. Some researchers have suggested that peritoneal fluid is not an innocent bystander, but rather an active promoter of growth of endometrial deposits by lipid peroxidation.[78, 79] Several cytokines, including TNFα and IL6, as well as lipid peroxidation could be targets for treatment.[70]

Thiazolidinediones, ligands of peroxisome proliferator-activated receptor (PPAR) γ2, inhibited monocyte migration in a mouse model of endometriosis.[80] These drugs are traditionally used for treatment of type 2 diabetes mellitus and have immunosuppressive effects. If the inhibition found in mice also occurs in women, thiazolidinediones could find a new indication in the treatment of endometriosis.[70]

Endometriotic lesions show high oestradiol biosynthesis and low oestradiol inactivation compared with endometrium from unaffected women.[81, 82] Aromatase is the key enzyme in the biosynthesis of oestradiol, catalysing conversion of androstenedione and testosterone, derived from ovarian and adrenal sources, to oestrone and oestradiol, respectively. Aromatase is expressed in ovarian granulosa cells, placental syncytiotrophoblasts, adipose tissue, skin fibroblasts, and brain, but is normally absent from endometrium. However, studies from Zeitoun *et al.* showed abnormal expression of aromatase in endometriotic lesions and in much lower levels in eutopic endometrium of women with endometriosis.[81] This abnormal expression is due to a stimulatory transcription factor that increases aromatase transcription, resulting in conversion of androstenedione to oestrone.[83] The latter is a weak oestrogen that is subsequently converted to the more potent oestradiol by 17γ-hydroxysteroid-dehydrogenase-1.

Inactivation of oestradiol is completed by 17γ-hydroxysteroid-dehydrogenase-2, normally present in endometrial glandular cells; however, in endometriosis the glandular cells lack this enzyme, leading to impaired inactivation of oestradiol and increased local concentrations of this steroid hormone.[82] Oestradiol stimulates production of prostaglandins, specifically PGE2, which further stimulates activity of aromatase. Thus, treatments for symptomatic endometriosis aimed at inhibiting ovarian oestradiol production (*e.g.* OCs, GnRHa) would give limited benefit to women with autonomous endometriotic oestradiol production.[83] Aromatase inhibitors offer an innovative approach to the treatment of this disorder,[84-86] and additional evidence suggests that these inhibitors, alone or in combination with more standard treatments, are successful in eradicating endometriotic lesions and improving pain symptoms when other medical therapies, such as GnRH agonists, have failed.[70]